Risk-Benefit: Key Innovations in the Document ICH M4E(R2)

Pictured above: Venous thrombosis

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Disclaimer

The views and opinions expressed in the following presentation are my personal views and opinions and not necessarily those of Janssen – Pharmaceutical Companies of Johnson & Johnson.
'Currently, regulatory agencies may make different decisions despite having the same data on new medicines submitted for their assessment, leading to increased pressure to improve agency transparency and accountability and to establish appropriate document governance for decision-making processes. A universal benefit-risk assessment framework applicable to pharmaceutical companies and regulatory agencies could serve as a standardized structured model for benefit-risk assessment to support transparency in decision making.'

History of Benefit-Risk Methodology

• The US Food, Drug and Cosmetic Act first embraced the idea of benefit versus risk in 1962 (the Kefauver-Harris Drug Amendments required that firms had to show a drug’s effectiveness before marketing)


• In 1998 CIOMS IV stated that ‘It is a frustrating aspect of benefit-risk evaluation that there is no defined and tested algorithm or summary metric that combines benefit and risk data and that might permit straightforward quantitative comparisons of different treatment options, which in turn might aid in decision making’

• Report of the CHMP working group on benefit-risk assessment models and methods (European Medicines Agency, January 2007)

• Today: EMA Effects table, FDA grid, and much more...
Revision of M4E (CTD): Scope

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

REVISION OF M4E GUIDELINE ON ENHANCING THE FORMAT AND STRUCTURE OF BENEFIT-RISK INFORMATION IN ICH

EFFICACY - M4E(R2)

Current Step 4 version
dated 15 June 2016

Module 2.5: Clinical Overview
2.5.1 Product Development Rationale
2.5.2 Overview of Biopharmaceutics
2.5.3 Overview of Clinical Pharmacology
2.5.4 Overview of Efficacy
2.5.5 Overview of Safety
2.5.6 Benefits and Risks Conclusions
2.5.7 Literature References
Revision of M4E (CTD): Rationale

- Benefit-risk assessment is the fundamental basis of regulatory decision-making

- Both regulators and industry have developed approaches for structured benefit-risk assessment
  - E.g. EMA assessment report and effects table, FDA template, PhRMA BRAT framework, IMI PROTECT

- No structure is suggested in the current guideline that could aid industry in structuring their benefit-risk assessment
  - A high degree of variability in the approaches taken by applicants

- Harmonisation of the format and structure of benefit-risk assessments in regulatory submissions could result in reduced regulatory and industry burden and enhanced communication between regulators and applicants
Revision of M4E (CTD): Aspects not Addressed

- The approach or process to be applied by regulators in conducting the benefit-risk assessment

- Issues that are related to how a regulator reaches a specific conclusion on benefit-risk information
Revision of M4E (CTD): the New Proposed Structure

2.5.6.1 Therapeutic context

2.5.6.4 Benefit-risk assessment

2.5.6.3 Risks

2.5.6.2 Benefits
Therapeutic Context Section: Key Features

- Disease or condition
  - Description of the aspects of the disease/condition that are most relevant or have the greatest impact on the intended population

- Current therapies
  - Description of the major therapies in the intended population and the medical need for the new therapy

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2_Step_4.pdf
Benefits Section: Key Features

- Should summarize **key benefits**
  - Favorable effects generally assessed by primary and other clinically important endpoints across the studies in a development program
  - Benefits may also include important characteristics of the medicinal products (e.g. convenience, herd immunity)

- Should include an analysis of the strengths, limitations and uncertainties of the evidence
  - E.g. study design considerations, number of clinical studies and consistency of results across studies, generalizability of the clinical study data to clinical practice

[http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2_Step_4.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2_Step_4.pdf)
Risks Section: Key Features

- Should summarize key risks
  - Exhaustive definition of risk
  - Key risk = unfavorable effect that is important from a clinical and/or public health perspective in terms of its frequency and/or severity

- Should include an analysis of the strengths, limitations and uncertainties of the evidence
  - E.g. number of patients and duration of exposure, number of patients in relevant subpopulations

- Should discuss the proposed approach to managing each key risk

[http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2__Step_4.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2__Step_4.pdf)
Benefit-Risk Assessment Section: Key Features

The most important section: the applicant’s conclusion on the benefit-risk

Requires the applicant’s

- interpretation of the benefit and risk data (clinical judgment) and of uncertainties
- weighing of the key benefits and key risks

Possible methods:

- Descriptive approach generally adequate
- Methodologies that quantitatively express the underlying judgments and uncertainties are optional

Additional tools:

- Summary tables and graphical displays
- Information about the patient perspective including patient preference studies

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2_Step_4.pdf
IMI PROTECT WP5: a Systematic Review and Classification of Available Methodologies

Enhanced benefit-risk guidance in the ICH M4E guideline

Enhanced expression of the benefit-risk profile and conclusions in the CTD Clinical Overview

Enhanced expression of benefit-risk decisions by regulatory authorities, and more transparency